REMARKS

Status of the Claims.

Claims 101-106, 108-141, and 173-175 are pending with entry of this amendment, claims 1, 107, and 142-172 being cancelled herein, and claims 173-175 being added. Claims 101, 108, and 125-127 are amended herein. Support for the amendment of claim 101 and for new claims 173 and 174 is found at least in the specification at page 24, lines 14-23 and in Figure 2B. Support for new claim 175 is found at least at page 5, lines 10-13 of the specification. Therefore, these amendments introduce no new matter.

35 U.S.C. §102.

Lu and Negrin

Claims 101-110, 118-120, 122-128, and 131-141 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lu and Negrin. Office Action, page 2. This rejection is respectfully traversed.

In explaining the rejection, the Examiner stated:

> [A]pplicant has not provided any objective evidence to indicate that the cell line instantly claimed in [*sic*] *materially* different or distinct from that taught by Lu *et al.* It appears that the methodology of making the cell line as disclosed by Lu *et al* and that of the instant application are identical and would therefore lead to the same product.

Id. at pages 6-7. In view of the amendments to the claims, both of these statements are incorrect.

The only pending independent claim, claim 101 recites:

> A composition comprising an ex vivo expanded population of cytotoxic lymphocytes having the ability to kill tumor-associated vasculature cells, and a pharmaceutically acceptable carrier, wherein said population is produced by expanding lymphocytes in a closed system with agitation, and said population has a cytotoxic activity characterized in that specific lysis of cancer cells significantly exceeds that of a population of cells produced by growing the

same lymphocytes in a standard flask, as measured in a ^{51}Cr-release assay wherein the population is added to said cancer cells at a ratio of 10:1.

As a threshold matter, Applicant respectfully point out that the claimed invention is a population of cells, and not a cell line. As those of skill in the art readily appreciate from the plain language of the claims and from the specification, a population of cells need not be clonal and, in fact, can be a heterogenous mixture of multiple cell types.

As has been pointed out repeatedly throughout the prosecution of this application, Lu teaches or suggests nothing regarding a "population of cytotoxic lymphocytes having the ability to kill tumor-associated vasculature cells," as recited in claim 101. The §102 rejection is based on the Examiner's contention that Lu used a similar method to produce a population of cytotoxic lymphocytes to the method described in the specification for producing the claimed population. Accordingly, the Examiner argues that the ability to kill tumor-associated vasculature cells would be expected to be an inherent property of Lu's population absent evidence to the contrary.

The claims have been amended to clarify that the claimed population and the cells produced by Lu are produced by different methods and are, in fact, materially different populations. Lu's "cytokine-induced killer (CIK)" cells were grown in standard tissue culture flasks, as was conventional for lymphocyte cultures in 1994. By contrast, as recited in claim 101, the claimed population "is produced by expanding lymphocytes in a closed system with agitation," e.g., using a bioreactor. Prior to the filing date of the application, lymphocytes were not standardly grown in closed systems with agitation, and efforts to expand cytotoxic lymphocytes in bioreactors were not generally successful. Accordingly, this difference in the methods used to produce Lu's cells and the claimed population would be viewed as a material difference by anyone skilled in the art.

Furthermore, Applicant's specification contains evidence the claimed cell population had a materially different activity than Lu's cells. In particular, as shown in Figure 2B, cells grown in a closed system with agitation show significantly higher specific lysis of cancer cells, as measured in a ^{51}Cr-release assay when added to said cancer cells at a ratio of 10:1. The closed system-grown cells had a 35% higher specific lysis of cancer cells than cells grown in standard flasks. This is a material difference in the context of the invention, which was to prepare a population of cells suitable for immunotherapy. More specifically, a significant increase in cytotoxic activity of the cells allows the

clinician to reduce the number of cells that needed to be infused to treat a patient's cancer, which reduces the risk of stroke.

Thus, claim 101 defines a population of cells that is produced by a materially different method and has a materially different anti-tumor activity. For this reason, claim 101 clearly distinguishes the Lu reference.

Claim 101 also distinguishes the Lu reference based on its recitation of "the ability to kill tumor-associated vasculature cells." The ability to kill tumor-associated vasculature cells, while sparing normal vasculature cells, had never previously been described for any population of cells. The Examiner's argument that this property was inherent in Lu's cells cannot properly be maintained now that claim 1, on its face, defines a population of cells that is materially different from Lu's. According to the M.P.E.P., a "prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." M.P.E.P. § 2112.01 (citing *In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977)). Applicant has meet this burden by establishing that the claimed population is different from Lu's with respect to anti-tumor activity. As those of skill readily appreciate, once it is established that Lu's cells represented a different population than the claimed population, there is simply no credible scientific basis for assuming that Lu's cells ***necessarily*** had "the ability to kill tumor-associated vasculature cells," as recited in claim 101. It is well-settled that "[i]nherency . . . may not be established by probabilities or possibilities." *Continental Can Co. USA, Inc.* v. *Monsanto Co.,* 948 F.2d 1265, 1268-69 (Fed. Cir. 1991) (quoting *In re Oelrich,* 666 F.2d 578,581 (C.C.P.A. 1981)). For this additional reason, then, claim 101 is clearly patentable over Lu.

All of the remaining rejected claims depend, directly or indirectly, from claim 101 and are thus distinguished from Lu for at least the reasons discussed above. Accordingly, withdrawal of the § 102 rejection over Lu is respectfully requested.

Alvernas et al.

Claims 101-110, 122-128, and 131-141 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Alvernas et al. Office Action, page 6. This rejection is respectfully traversed.

Alvernas describes studies performed on "CIK" cells, which, as the abstract indicates had been previously described by the Negrin laboratory at Stanford University. This is the same laboratory that published Lu and Negrin earlier. Alvernas teaches that the disclosed CIK cells were

"generated through the sequential stimulation of human mononuclear cells with interferon-γ, the anti-CD3 MAb OKT3 and IL-2" and describes no variation in the procedure for producing CIK cells that is disclosed in the Lu reference. Accordingly, one skilled in the art would conclude that Alvernas' cells were grown in standard tissue culture flasks and had relatively low anti-tumor cytotoxic activity.

Therefore, the distinctions discussed above for the Lu reference also apply to the Alvernas reference. First, claim 101 recites a cell population "produced by expanding lymphocytes in a closed system with agitation," rather than in a standard flask. Second, claim 101 recites that this cell "population has a cytotoxic activity characterized in that specific lysis of cancer cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask, as measured in a ^{51}Cr-release assay wherein the population is added to said cancer cells at a ratio of 10:1." Finally, the record manifestly fails to provide any basis for assuming that Lu's cells ***necessarily*** had "the ability to kill tumor-associated vasculature cells." Because Alvernas fails to teach these elements of claim 101, explicitly or inherently, claim 101 clearly distinguishes Alvernas.

The remaining rejected claims are distinguished for Alvernas at least by virtue of their dependence from claim 101. Withdrawal of the § 102 rejection over Alvernas is therefore respectfully requested.

Conclusion.

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4160.

Beyer Weaver LLP
500 12th Street, Suite 200
Oakland, CA 94607
tel: (510) 663-1100
fax: (510) 663-0920

Respectfully submitted,

/Emily Haliday/

Emily M. Haliday
Reg. No: 38,903